(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068751 A1

(51) International Patent Classification[7]: C07D 223/16, 409/12, A61K 31/55, A61P 3/04, 25/06, 25/08, 25/22, 25/24, 25/28, 25/30

(21) International Application Number: PCT/EP03/01543

(22) International Filing Date: 13 February 2003 (13.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0203437.9	13 February 2002 (13.02.2002)	GB
0204758.7	28 February 2002 (28.02.2002)	GB
0212548.2	30 May 2002 (30.05.2002)	GB
0219711.9	23 August 2002 (23.08.2002)	GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BROMIDGE, Steven, Mark** [GB/IT]; GlaxoSmithKline SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **JOHNSON, Christopher, Norbert** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **MOSS, Stephen, Frederick** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **RAHMAN, Shahzad, Sharooq** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **WITTY, David, R** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **VALENTINE, Jill, Barbara**; GlaxoSmithKline, CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

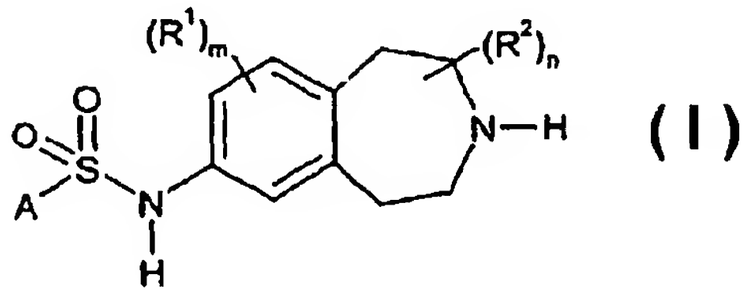
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/068751 A1

(54) Title: 7-ARYLSULFONAMIDO-2,3,4,5-TETRAHYDRO-1H-BENZO'DIAZEPINE DERIVATIVES WITH 5-HT6 RECEPTOR AFFINITY FOR THE REATMENT OF CNS DISORDERS



(I)

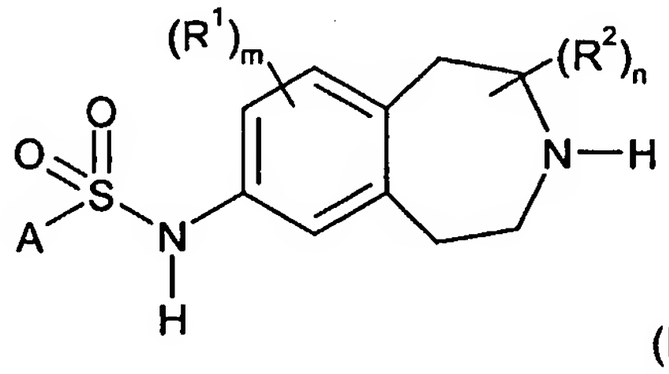
(57) Abstract: The present invention relates to novel sulfonamide compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

7-ARYLSULFONAMIDO-2,3,4,5-TETRAHYDRO-1H-BENZO'D!AZEPINE DERIVATIVES WITH 5-HT6 RECEPTOR AFFINITY FOR THE TREATMENT OF CNS DISORDERS

This invention relates to novel sulfonamide compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081, WO 99/02502, WO 99/37623, WO 99/42465 and WO 01/32646 (SmithKline Beecham plc) disclose a series of aryl sulphonamide and sulphoxide compounds that are said to be 5-HT_6 receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders.

A structurally novel class of compounds has now been found which possess affinity for the 5-HT_6 receptor. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents hydrogen, halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^3R^4$ or $SO_2NR^3R^4$, wherein R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

R^2 represents hydrogen or C_{1-6} alkyl;

m represents an integer from 1 to 3;

n represents an integer from 1 to 4;

A represents phenyl, naphthyl or a monocyclic or bicyclic heteroaryl group each of which may be optionally substituted by one or more substituents which may be the same or different, and which are selected from those defined for R^1;

or solvates thereof.

Specific groups of compounds of formula (I) which may be mentioned are those as defined above with the proviso that when A represents phenyl substituted at the 4-position, said substituent is not trifluoromethyl, trifluoromethoxy, C_{3-6} alkyl or C_{1-6} alkoxy.

Further specific groups of compounds of formula (I) which may be mentioned are those as defined above wherein m represents 0.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" is intended to mean a 5 or 6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

Preferably, A is substituted by 0 to 3 substituents, more preferably 0, 1 or 2 substituents.
Preferably, A represents phenyl or a monocyclic heteroaryl group (such as thienyl) optionally substituted by one or more halogen (such as chlorine or bromine, eg. 3-chlorophenyl, 4-chlorophenyl, 4-bromophenyl, 5-bromophenyl, 2,3-dichlorophenyl or 3,5-dichlorophenyl), C_{1-6} alkyl (such as methyl, eg. 4-methyl or ethyl, eg. 2-ethyl), C_{1-6} alkoxy (such as methoxy, eg. 2-methoxy), trifluoromethoxy (such as 2-trifluoromethoxy) or trifluoromethyl (such as 3-trifluoromethyl) groups.
More preferably, A represents unsubstituted phenyl or phenyl substituted by 3-trifluoromethyl, halogen (eg. 4-chloro and 4-bromo) and/or 2-trifluoromethoxy.
Most preferably, A represents phenyl di-substituted by halogen (especially 4-chloro or 4-bromo) and 2-trifluoromethoxy.
Preferably, m is 0 or 1, most preferably 0.
When m is 1, R^1 is preferably halogen (eg. 6-chlorine, 9-chlorine or 9-bromine) or C_{1-6} alkoxy (such as methoxy, eg. 8-methoxy).
Preferably, n is 0.

Preferred compounds according to the invention include examples E1-E17 as shown below, or a pharmaceutically acceptable salt thereof.

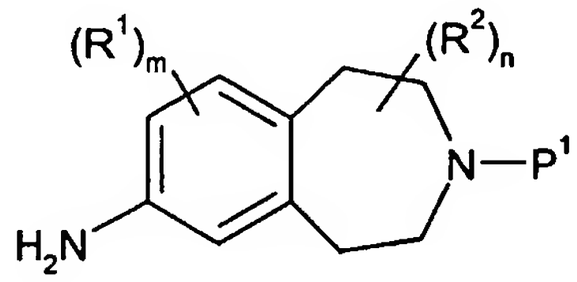
The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms. Preferably, the compound of formula (I) forms an acid addition salt with hydrochloric acid.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

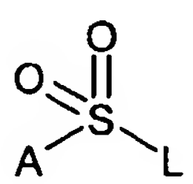
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

wherein R^1, R^2, m and n are hereinbefore defined and P^1 is a suitable protecting group such as acetyl, trifluoroacetyl, *t*-butyloxycarbonyl, 2',2',2'-trichloroethoxycarbonyl, benzyl or methyl, with a compound of formula (III)



(III)

wherein A is as hereinbefore defined and L is a suitable leaving group, such as a halogen atom (eg. fluorine or chlorine) and thereafter deprotecting the resultant compound; or

(b) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(c) interconversion to other compounds of formula (I).

Process (a) typically comprises the use of a suitable base such as pyridine or triethylamine in an inert solvent such as dichloromethane or tetrahydrofuran.

In process (b), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. Examples of process (c) include interconversions of the groups R^1, R^2 and A.

Compounds of formula (II) and (III) are known in the literature or can be prepared by analogous methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT_6 receptor and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the

treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Compounds of the invention are also expected to be of use in the treatment of obesity.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, obesity and cognitive memory disorders

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the

vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

3-*t*-Butyloxycarbonyl-7-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D1)

A solution of di-*t*-butyl dicarbonate (19.3g, 88.2mmol) in dichloromethane (150ml) was added over 0.5h to a stirred, ice-cooled solution of 7-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (11.3g, 58.8mmol) (for synthesis see Pecherer *et al.*, *J.Het. Chem.*, 1971, **8**, 779) and triethylamine (12.3ml, 88.2mmol) in dichloromethane (150ml) under argon. The solution was warmed to ambient temperature and stirred for 18h. The reaction mixture was then washed with water (2 x 400ml), dried ($MgSO_4$) and concentrated *in vacuo* to an oily solid. The solid was purified by chromatography over silica gel eluting with a solvent gradient of ethyl acetate/hexane to afford the title compound (D1) as a colourless solid (9.1g, 31.1mmol, 53%). δH ($CDCl_3$, 400MHz) 1.49 (9H, s), 3.00 (4H, br s), 3.58 (4H, br s), 7.27-7.29 (1H, br d), 7.98- 8.00 (2H, br, m).

Description 2

7-Amino-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D2)

A solution of 3-*t*-butyloxycarbonyl-7-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D1) (8.0g, 27.4mmol) in ethanol (250ml) was stirred with 10% palladium on carbon (1.3g) for 20h under one atmosphere of hydrogen at ambient temperature. The reaction mixture was filtered to remove the catalyst and the filtrate was evaporated *in vacuo* to yield the title compound (D2) as a colourless oil (7.0g, 26.6mmol, 97%). δH ($CDCl_3$, 400MHz) 1.48 (9H, s), 2.78 (4H, br s), 3.51 (6H, br s), 6.45-6.48 (2H, m), 6.89 (1H, d, J = 7.5Hz).

Description 3

3-*t*-Butyloxycarbonyl-7-(3-trifluoromethyl)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D3)

A solution of 7-amino-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D2) (512mg, 1.95mmol) in dichloromethane (20ml) was treated successively with pyridine (1ml) and 3-trifluoromethylbenzenesulfonyl chloride [Lancaster] (2.15 mmol, 520mg) with stirring. After 2 hours, water (1ml) was added, and the mixture stirred vigorously for a further 2h then the solvents evaporated. The residue was dissolved in ethyl acetate (100ml) and washed successively with 5% aq. citric acid (50ml), water (50ml) and brine (50ml) then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography (gradient of ethyl acetate/hexane) on silica gel to afford the title compound (D3) as a clear oil (910mg, 99%).
δH ($CDCl_3$, 400MHz) 1.47 (9H, s), 2.77-2.83 (4H, m), 3.48-3.49 (4H, m), 6.8 (1H, br s), 6.9 (1H, br s), 6.99 (1H,d), 7.23 (1H, s), 7.60 (1H, app.t), 7.79 (1H, d), 7.95 (1H, d), 7.98 (1H, s).

Description 4

3-*t*-Butyloxycarbonyl-7-phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D4)

The title compound (D4) was prepared in 72% yield as described in Description 3, by treatment of 7-amino-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D2) with phenyl sulfonyl chloride.
δH (D6-DMSO), 400MHz) 1.37 (9H, s), 2.70 (4H, br, s), 3.36 (4H, br, s), 6.83-6.85 (2H, m), 6.97 (1H, d, J = 8.3 Hz), 7.52-7.60 (3H, m), 7.75 (2H, d, J = 7.2Hz), 10.2 (1H, s).

Description 5

7-Nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D5)

To a stirred, ice-cooled solution of 7-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (29g, 0.15mol) (for synthesis see Pecherer *et al.*, *J.Het. Chem.*, 1971, 8, 779) in dichloromethane (1 litre) was slowly added triethylamine (41.8ml, 0.30mol) followed by dropwise addition of trifluoroacetic anhydride (42.4ml, 0.30mol). The resulting mixture was allowed to stir and warm to ambient temperature over 18h before being poured onto ice. The organic phase was separated and the aqueous layer extracted with dichloromethane (200ml). The combined organic phases were then washed with saturated aqueous sodium hydrogen carbonate (600ml), brine (600ml) and then dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue (59g) was purified by column chromatography on silicagel eluting with ethyl acetate/ hexane (1:4) to afford the title compound (D5) as a yellow solid (37g, 0.128mol, 86%).
δH ($CDCl_3$, 400MHz) 3.08-3.13 (4H, m), 3.74-3.84 (4H, m), 7.31-7.36 (1H, m), 8.03- 8.07 (2H, m).

Description 6

7-Amino-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D6)

A mixture of 7-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D5) (37g, 0.128mmol) and 10% palladium on carbon (5g) in ethanol (200ml) and 1,4-dioxane (600ml) was stirred with hydrogen at atmospheric pressure and room temperature for 18h. The mixture was filtered and the filtrate concentrated *in vacuo* to a solid which was stirred with hexane (200ml) for 1h. Filtration of the mixture gave the title compound (D6) as a solid (32.5g, 0.126mmol, 98%).

δH ($CDCl_3$, 400MHz) 2.84-2.89 (4H, m), 3.05 (2H, br, s), 3.63-3.68 (2H, m), 3.71-3.76 (2H, m), 6.48-6.51 (2H, m), 6.91-6.95 (1H, m).

Description 7

7-(4-Bromo-2-trifluoromethoxy)phenylsulfonamido-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D7)

To a stirred solution of 7-amino-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D2) (23.4g, 89.3mmol) in pyridine (60ml) and dichloromethane (140ml) at 5°C was added 2-trifluoromethoxy-4-bromo-benzenesulfonyl chloride (33.4g, 98.2mmol) in dichloromethane (20ml) over 30 mins. The solution was then stirred at room temperature for 18 hours. The solvents were removed and the residue purified by chromatography on silica using 20% ethyl acetate in hexane. The crude product was recrystallised from ethyl acetate / hexane to afford the title compound (D7) as a pale yellow solid (30.5g, 60%).

δH ($CDCl_3$, 400MHz), 1.46 (9H, s), 2.79 (4H, m), 3.48 (4H, m), 6.63 (1H, s), 6.80 (1H, br s), 6.84 (1H, s), 6.96 (1H, d, J=8.08 Hz), 7.47 (1H, dd J=8.4, 1.6 Hz), 7.52 (1H, s), 7.79 (1H, d J=8.4Hz).

Description 8

7-(4-Bromo-2-trifluoromethoxy)phenylsulfonamido-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D8)

A solution of 4-bromo-2-trifluoromethoxybenzene sulfonyl chloride (42.4g, 125mmol) in dichloromethane (100ml) was added over 20 minutes to a stirred solution of 7-amino-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D6) (32.3g, 125mmol) and pyridine (30.2ml, 375mmol) in dichloromethane (150ml) at room temperature under argon. After 18h the solution was diluted with dichloromethane (750ml) and washed successively with water (1 litre), 1M hydrochloric acid (2 x 1 litre) and brine (1 litre). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to a red oil which was purified by column chromatography over silicagel eluting with a gradient of ethyl acetate/hexane to afford the title compound (D8) as a colourless oil (56g, 100mmol, 80%)

δH ($CDCl_3$, 400MHz) 2.87-2.91 (4H, m), 3.62-3.65 (2H, m), 3.70-3.73 (2H, m), 6.67 (1H, br, s), 6.83-6.86 (1H, m), 6.91 (1H, d, J = 2.2Hz), 6.99-7.03 (1H, m), 7.48-7.58 (2H, m), 7.79-7.82 (1H, m).

Found $[MH]^+$ 561/563 ($C_{19}H_{15}BrF_6N_2O_4S$)

Description 9

7-(4-Chloro-2-trifluoromethoxy)phenylsulfonamido-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D9)

An efficiently stirred mixture of 7-(4-bromo-2-trifluoromethoxy)phenylsulfonamido-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D8) (55g, 98mmol) and copper (I) chloride (193g, 1.94mol) in dry N,N-dimethylformamide (540ml) was heated at 120°C for 24h under argon. The mixture was cooled to ambient temperature then the solid filtered, and washed with dry *N,N*-dimethylformamide (2 x 100ml). To the filtrate and washings was added fresh copper (I) chloride (48g, 485mmol) and the stirred mixture reheated at 120°C for 18h under argon. The mixture was cooled to ambient temperature and the solid was filtered and washed with dichloromethane (6 x 200ml). The filtrate and washings were concentrated *in vacuo* and the residue re-concentrated with toluene (2 x 750ml). The residue was then stirred with dichloromethane (250ml) and the whole mixture filtered through kieselguhr. The filtrate was concentrated *in vacuo* and the residue partially purified by column chromatography over silicagel eluting with dichloromethane to afford crude title product (D9) as a foam (42.8g). This material was crystallised by dissolving in diethyl ether (150ml) at room temperature and adding hexane (150ml) with stirring and leaving to fully crystallize for 2 days. The colourless crystals were filtered off and identified as the title compound (D9) (24g, 46.4mmol, 47%). A second crop of the product (D9) (7.4g, total yield = 31.4g, 60.7mmol, 62%) was isolated from the filtrate by concentrating the filtrate and re-chromatographing the residue over silicagel (acetone/toluene gradient) followed by crystallisation from diethyl ether / hexane.

δH ($CDCl_3$, 400MHz) 2.87-2.91 (4H, m), 3.62-3.65 (2H, m), 3.70-3.73 (2H, m), 6.71 (1H, s), 6.83-6.87 (1H, m), 6.90 (1H, d, J = 2.3Hz), 6.99-7.03 (1H, m), 7.31-7.39 (2H, m), 7.87-7.90 (1H, m).

Found $[MH]^+$ 517/519 ($C_{19}H_{15}ClF_6N_2O_4S$)

Description 10

7-Amino-6-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid tert-butyl ester (D10)

7-Amino-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (D2) (1.57g, 6mmol) was dissolved in acetonitrile (30ml) and treated with N-chlorosuccinimide (895mg, 6.5mmol) at 0°C and the stirred mixture allowed to warm to room temperature for 14 hours. Saturated aqueous sodium sulphite (5ml) was added and the mixture evaporated. The residue was triturated with diethyl ether (2 x 100ml), and the combined organic phase dried ($MgSO_4$), filtered and evaporated. The residue was subjected to flash chromatography on silica gel, eluting with a mixture of ethyl acetate and hexane to afford the title compound (D10) as a white solid; yield 305mg.

δH ($CDCl_3$, 400MHz) 1.46(9H, s), 2.82 (2H, m), 3.12 (2H, m), 3.53 (4H, m), 4.02 (2H, s), 6.56 (1H, d), 6.82 (1H, d).

Description 11

3-Acetyl-6-iodo-8-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D11)

To a stirred solution of 3-acetyl-7-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine [J. Heterocyl. Chem. (1971), **8(5)**, 779-783] (2.71g, 11. 6mmol) in trifluoromethane-sulfonic acid (15ml) at room temperature was added *N*-iodosuccinimide (3.38g, 15mmol), portionwise over 1 hour, then the mixture stirred for 2 days. The mixture was poured onto ice and extracted with dichloromethane. After separating, the organic layer was washed with sodium thiosulfate solution, then brine and dried over magnesium sulfate. After filtration, the solvent was evaporated *in vacuo* to afford the title compound (D11), (2.74g, 69%).
δH ($CDCl_3$, 400MHz), 2.17,2.16 (3H, 2s), 3.10 (2H, m), 3.30 (2H, m), 3.65 (2H, m), 3.76 (2H, m), 8.00 (1H, 2d, J = 2.2Hz), 8.60 (1H, 2d, J = 2.2Hz).

Description 12

6-Iodo-8-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D12)

A mixture of 3-acetyl-6-iodo-8-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D11) (2.74g, 7.59mmol) and hydrochloric acid (36%, 250ml) was heated at reflux for 2 days, cooled, filtered and evaporated to dryness. The residue was redissolved in water, treated with sodium bicarbonate and extracted with dichloromethane. The organic layer was dried, filtered and evaporated to afford the title compound (D12) (2.2g, 91%).
δH (DMSO-d6, 400MHz), 2.50 (4H, m), 3.04 (2H, m), 3.22 (2H, m), 8.02 (1H, d, J=2.4Hz), 8.40 (1H, d, J=2.4Hz).

Description 13

6-Iodo-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D13)

To a stirred solution of 6-iodo-8-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D12) (2.2g, 6.9mmol) in dichloromethane (40ml), was added 2 equivalents of polymer supported Hunig's base [Argonault Tech.] (3.83mmol/g; 3.6g, 13.8mmol). After cooling to 5°C, trifluoroacetic anhydride (1.6g, 7.61mmol) was added dropwise, then stirred at room temperature for 18 hours. After filtration, the solution was washed with water then dried over magnesium sulfate. After filtration, the solvent was removed and the residue purified by chromatography on silica using 25% diethyl ether in hexane to afford the title compound (D13) (2.56g 90%).
δH ($CDCl_3$, 400MHz) 3.17 (2H, m), 3.38 (2H, m), 3.75 (4H, m) 8.01 (1H, m) 8.61 (1H, m).

Description 14

6-Chloro-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D14)

A mixture of 6-iodo-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D13) (222mg, 0.5mmol), copper (I) chloride (362mg, 3.65mmol) and dimethyl formamide (5ml) were heated to 110 °C for 18 hours with stirring. The solvent was removed and the residue purified by chromatography on silica using 25% diethyl ether in hexane to afford the title compound (D14), (130mg, 75%)
δH ($CDCl_3$, 400MHz) 3.15 (2H, m), 3.48 (2H, m), 3.76 (2H, m), 3.82 (2H, m), 7.95 (1H, m) 8.19 (1H, m).

Description 15

6-Bromo-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D15)

Prepared from 6-iodo-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D13) and copper (I) bromide in a similar manner to Description 14, in 41% yield.
δH ($CDCl_3$, 400MHz) 3.18 (2H, m), 3.37 (2H, m), 3.60-3.85 (4H, m), 7.97-8.06 (1H, m), 8.36-8.37 (1H, m).

Description 16

8-Amino-6-chloro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D16)

6-Chloro-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D14) (1.7g, 5.27mmol), was dissolved in methanol (20ml) and treated with 6 equivalents of titanium trichloride (30% solution in 2N HCl, 12.3ml, 5.27mmol) at room temperature with stirring, which was continued for a further hour. The reaction was treated with dropwise 30% hydrogen peroxide until the purple colour was extinguished, toluene added and the solvent removed. A saturated solution of sodium acetate in methanol was added until the pH rose to ~5 then the solvent was removed. The residue was purified by chromatography on silica using 20-50% diethyl ether in hexane to afford the title compound (D16) (975mg, 63%).
δH ($CDCl_3$, 400MHz) 2.89 (2H, m), 3.11 (2H, m), 3.5 (2H br.s), 3.63-3.76 (4H, m), 6.38 (1H, m), 6.62 (1H, m).

Description 17

8-Amino-6-bromo-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D17)

Prepared from 6-bromo-8-nitro-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D15) in a similar manner to Description 16, in 34% yield.
δH ($CDCl_3$, 400MHz) 2.0 (2H, br.s) 2.89 (2H, m), 3.16 (2H, m), 3.64-3.76 (4H, m), 6.42 (1H, m) 6.81 (1H, m).

Description 18

7-Hydroxy-8-nitro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D18)

7-Hydroxybenzazepine [WO 00/21951] (40g, 0.15 mol), was dissolved in glacial acetic acid (400ml) and added dropwise to a mixture of glacial acetic acid (200ml), acetic anhydride (20ml) and 70% nitric acid (16g). The reaction temperature was maintained at 10°C using an ice bath. Following addition, the mixture was allowed to warm to ambient and stirrer for a further 2 hours. The mixture was poured into ice/water (1 litre) and dichloromethane (2 litres) added. The organic phase was separated and neutralised to pH6 by addition of saturated sodium bicarbonate solution. The organic phase was separated, dried ($MgSO_4$) and purified by chromatography [Biotage Flash 75, 2Kg silica cartridge] using ethyl acetate and hexane as eluents to give the title compound (D18) in 52% yield.
δH ($CDCl_3$, 400MHz) 1.48 (9H, s), 2.89 (4H, m), 3.56 (4H, m), 6.92 (1H, s), 7.84 (1H, s), 10.5 (1H, br.s).

Description 19

7-Methoxy-8-nitro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D19)

A mixture of 7-hydroxy-8-nitro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D18) (49g, 0.16 mol), methyl iodide (12.4ml), potassium carbonate (27.4g) in N,N-dimethylformamide (400ml) was stirred at room temperature for 16 hours. The mixture was poured into water (300ml) and extracted with diethyl ether (3 x 300ml), the combined organic phases washed with brine (50ml) and dried over $MgSO_4$ to afford the title compound (D19) in 96% yield.
δH ($CDCl_3$, 400MHz) 1.49 (9H, s), 2.88 (2H, m), 2.94 (2H, m), 3.57 (4H, m), 3.94 (3H, s), 6.84 (1H, s), 7.67 (1H, s).

Description 20

8-Amino-7-methoxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D20)

A solution of 7-methoxy-8-nitro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D19) (25g, 78mmol) in ethanol (700ml) was treated with 5% palladium on charcoal (5g) and hydrogenated at 50psi for 1 hour. The catalyst was removed by filtration under argon and the solution evaporated to give the title compound (D20) as a white solid in 96% yield.
δH ($CDCl_3$, 400MHz) 1.48 (9H, s), 2.76 (4H, m), 3.51 (4H, m), 3.65 (2H, brs), 3.82 (3H, s), 6.50 (1H, s), 6.55 (1H, s).

Description 21

7-(3,5-Dichloro-2-methoxy-benzenesulfonylamino)-8-methoxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D21)

8-Amino-7-methoxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D20) (80mg) was dissolved in pyridine (0.5ml), cooled to 0°C and treated with 3,5-dichloro-2-methoxy-benzenesulfonyl chloride (110mg, 0.41mmol). After 16 hours, the solution was treated with methanol-water 1:1 (1ml) and evaporated. The residue was subjected to chromatography on silicagel, eluting with hexane and diethyl ether to give the title compound (D21) in 87% yield.
δH ($CDCl_3$, 400MHz) 1.46 (9H, s), 2.78 (4H, m), 3.48 (4H, m), 3.71 (3H, s), 3.87 (3H, s), 6.53 (1H, brs), 7.22 (1H, s), 7.46 (2H, app.s), 7.49 (1H, s).

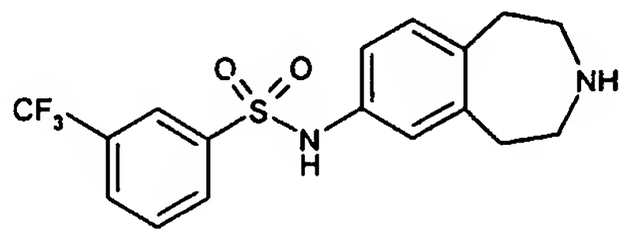
Description 22

7-(4-Bromo-2-trifluoromethoxy-benzenesulfonylamino)-6-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid tert butyl ester (D22)

A solution of 7-amino-6-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid tert-butyl ester (D10) (0.25mmol, 75mg) in dichloromethane (2ml) was treated with 4-bromo-2-trifluoromethoxy-benzenesulfonyl chloride (135mg 0.4mmol) in dichloromethane (2ml) and pyridine (0.2ml). After 14 hours, the solution was treated with water (0.5ml) and evaporated then the residue purified by flash chromatography on silicagel, eluting with diethyl ether and hexane to afford the title compound (D22) as a white solid.
δH ($CDCl_3$, 400MHz) 1.42 (9H, s), 2.85 (2H, m), 3.08 (2H, m), 3.48 (4H, m), 6.94 (1H, d), 7.33 (2H, m), 7.48 (2H, m), 7.85 (1H, d).

Example 1

2,3,4,5-Tetrahydro-7-(3-trifluoromethyl)phenylsulfonamido-1*H*-benzo[*d*]azepine, hydrochloride (E1)



.HCl

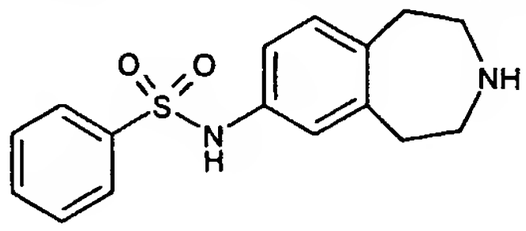
A suspension of 3-*t*-butyloxycarbonyl-7-(3-trifluoromethyl)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D3) (910mg, 1.93 mmol) in hydrochloric acid (40ml, 4M in 1:1 water : 1,4-dioxane) was warmed to 60°C for 1 hour. The now clear solution was concentrated *in vacuo* and the residue crystallised from methanol/ether to afford the title compound (E1) as a pale brown solid (700mg, 89%).

δH (MeOH, 400MHz) 3.05-3.09 (4H, m), 3.22-3.26 (4H, m), 6.94 (1H, dd, J = 2.1, 8.1 Hz), 7.03 (1H, d, J = 2.1Hz), 7.12 (1H, d, J = 8.1 Hz), 7.73 (1H, app.t, J= 7.9Hz), 7.91 (1H, d, J = 7.8 Hz), 7.98 (1H, s), 8.03 (1H, d, J = 7.9Hz).

Found $[MH]^+$ 371 ($C_{17}H_{17}F_3N_2O_2S$).

Example 2

7-Phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, hydrochloride (E2)



.HCl

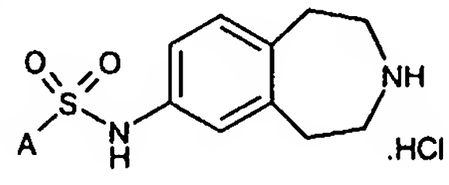
The title compound (E2) was prepared in 90% yield as described in Example 1, from 3-*t*-butyloxycarbonyl-7-phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D4).

δH (D6-DMSO, 400MHz) 2.98 (4H, br, s), 3.08 (4H, br, s), 6.87-6.93 (2H, m), 7.04 (1H, d, J = 8.1Hz), 7.53-7.63 (3H, m), 7.77 (1H, d, J= 7.3Hz), 930 (2H, br, s), 10.35 (1H, br, s).

Found $[MH]^+$ 303 ($C_{16}H_{18}N_2O_2S$).

Examples 3-5 (E3-E5)

Examples E3-E5 were prepared by a two step process, using the appropriate aryl sulfonyl chloride with 7-amino-3-t-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D2) in a similar manner to that described in Description 3, followed by a deprotection step in a similar manner to that described in Example 1.

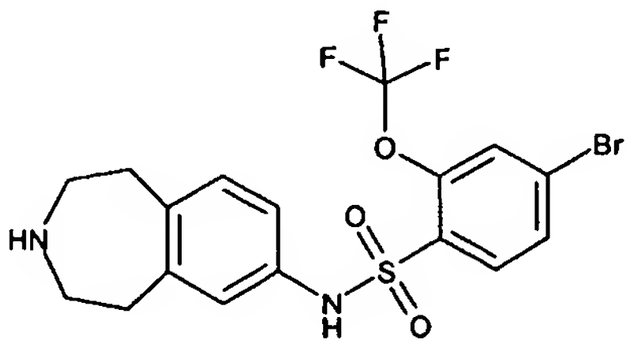


.HCl

Example	A	$[MH]^+$	Formula
E3	3-chlorophenyl	337/339	$C_{16}H_{17}ClN_2O_2S$
E4	5-bromo-2-thienyl	387/389	$C_{14}H_{15}BrN_2O_2S_2$
E5	4-methylphenyl	317	$C_{17}H_{20}N_2O_2S$

Example 6

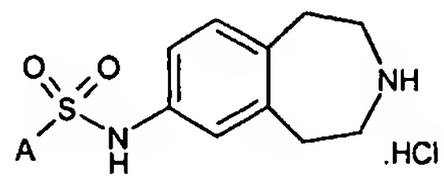
7-(4-Bromo-2-trifluoromethoxy)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E6)



Prepared in an analogous procedure to E1 from 7-(4-bromo-2-trifluoromethoxy)phenylsulfonamido-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (obtained in an analogous manner to that of D3 using 4-bromo-2-trifluoromethoxybenzenesulfonyl chloride).
Found $[MH]^+$ 465/467 ($C_{17}H_{16}BrF_3N_2O_3S$).

Examples 7-9 (E7-E9)

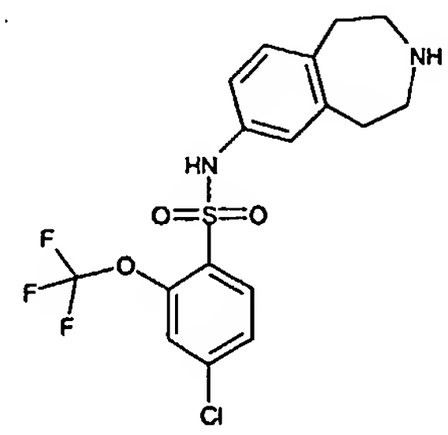
Examples E7-E9 were prepared by a two step process, using the appropriate aryl sulfonyl chloride with 7-amino-3-t-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D2) in a similar manner to that described in Description 3, followed by a deprotection step in a similar manner to that described in Example 1.



E7	2,3-dichlorophenyl	371/373	$C_{16}H_{16}Cl_2N_2O_2S$
E8	3,5-dichloro-2-methoxyphenyl	401/403	$C_{17}H_{18}Cl_2N_2O_3S$
E9	4-bromo-2-ethylphenyl	409/411	$C_{18}H_{21}BrN_2O_2S$

Example 10

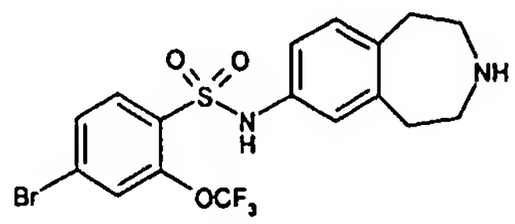
7-(4-Chloro-2-trifluoromethoxy)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E10)



Prepared from 7-(4-bromo-2-trifluoromethoxy)phenylsulfonamido-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (obtained by treatment of E6 with trifluoroacetic anhydride in the presence of pyridine as a base) by reaction with copper (I) chloride in *N,N*-dimethylformamide at reflux, followed by removal of the trifluoroacetyl group using aqueous ammonia.
Found $[MH]^+$ 421/423 ($C_{17}H_{16}ClF_3N_2O_3S$).

Example 11

7-(4-Bromo-2-trifluoromethoxy)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, hydrochloride (E11)



.HCl

7-(4-Bromo-2-trifluoromethoxy)phenylsulfonamido-3-*t*-butyloxycarbonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D7) (30.2g, 53.5mmol) in dioxane (175ml) and 4N hydrochloric acid (175ml) was heated to 90°C with stirring. After 90 mins a solution was formed and the solvents were removed *in vacuo*. The residue was recrystallised from isopropanol to afford the title compound (E11) (23.6g, 88%).

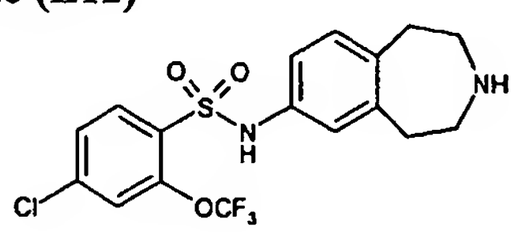
δH ($MeOd_4$, 400MHz) 3.04 (4H, m), 3.22 (4H, m), 6.92 (1H, dd, J=2.4Hz, 8Hz), 7.01 (1H, d, J=2.4Hz), 7.08 (1H,d, J=8Hz), 7.64, (2H, m), 7.88, (1H, d, J=8.8Hz).

Found $[MH]^+$ 465/467 ($C_{17}H_{16}BrF_3N_2O_3S$)

m.p. 231 - 233 °C

Example 12

7-(4-Chloro-2-trifluoromethoxy)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, hydrochloride (E12)



.HCl

To a stirred suspension of 7-(4-chloro-2-trifluoromethoxy)phenylsulfonamido-3-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (D9) (30.3g, 58.6mmol) in methanol (750ml) was added 32% ammonia solution (75ml) and the resulting solution stirred at room temperature for 24h. The reaction mixture was then evaporated *in vacuo,* then the residue was suspended in toluene (800ml) and solvent evaporated *in vacuo*. The residue was again suspended in toluene (800ml) and solvent evaporated *in vacuo*. To the resulting colourless residue was added diethyl ether (400ml) and the mixture stirred for 30 minutes before being filtered and dried *in vacuo* at 50 °C. To a suspension of this material in dichloromethane (250ml) was added 1M HCl/diethyl ether (123ml) followed by methanol (50ml). The resulting solution was concentrated to an oil and to this added dichloromethane (100ml)/diethyl ether (300ml) to give fine white crystals. The crystals were filtered, washed with dichloromethane/diethyl ether (1:3) (2x75ml) and diethyl ether (2x75ml) before being dried *in vacuo*. The material was then recrystallised from *iso*-propanol to afford the desired compound as a white solid (21.8g, 81%).

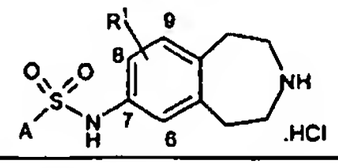
δH (DMSO-d_6, 400MHz) 2.99-3.01 (4H, m), 3.08 (4H, br s), 6.86 (1H, dd, J = 8.1Hz, 2.3Hz), 6.94 (1H, d, J = 2.2Hz), 7.07 (1H, d, J = 8.2Hz), 7.66-7.70 (2H, m), 7.97 (1H, d, J = 8.5Hz), 9.37 (2H, br s), 10.70 (1H, br s).

Found $[MH]^+$ 420/422 ($C_{17}H_{16}ClF_3N_2O_3S$)

m.p. 210 - 211 °C.

Examples 13-15 (E13-E15)

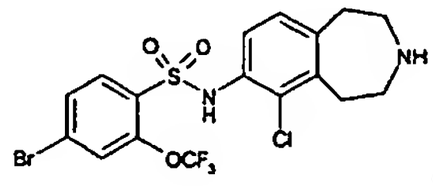
Examples E13-E15 were prepared by treatment of the appropriate trifluoroacetyl protected aminobenzo[*d*]azepine derivative (D16 for E13 and E14 and D17 for E15) with the required arylsulfonyl chloride in an analogous manner to the process described in D8, followed by treatment of the product with aqueous ammonia (2M), and subsequent purified by recrystallisation of their respective hydrochlorides.



Example	R^1	A	$[MH]^+$	Formula
E13	9-Cl	phenyl	337	$C_{16}H_{17}ClN_2O_2S$
E14	9-Cl	(3-trifluoromethyl)phenyl	405	$C_{17}H_{16}ClF_3N_2O_2S$
E15	9-Br	phenyl	381/383C	$C_{16}H_{17}BrN_2O_2S$

Example 16

7-(4-Bromo-2-trifluoromethoxy-benzenesulfonylamino)-6-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine Hydrochloride (E16)



.HCl

Prepared from 7-(4-bromo-2-trifluoromethoxy-benzenesulfonylamino)-6-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert* butyl ester (D22) by an analogous method to that described for Example 1.

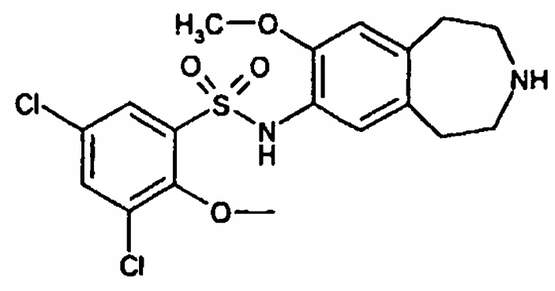
δH (MeOH-d_4, 400MHz) 3.15-3.47 (8H, m), 7.15 (1H, d), 7.39 (1H, d), 7.65, (2H, m), 7.89, (1H, d).

δH (MeOH-d_4, 400MHz) 3.15-3.47 (8H, m), 7.17 (1H, d), 7.37 (1H, d), 7.65, (2H, m), 7.82, (1H, d).

Found $[MH]^+$ 499, 501, 503 ($C_{17}H_{15}BrClF_3N_2O_3S$)

Example 17

3,5-Dichloro-2-methoxy-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)-benzenesulfonamide hydrochloride (E17)



. HCl

Prepared from 7-(3,5-dichloro-2-methoxy-benzenesulfonylamino)-8-methoxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester (D21) by an analogous method to that described for Example 1.

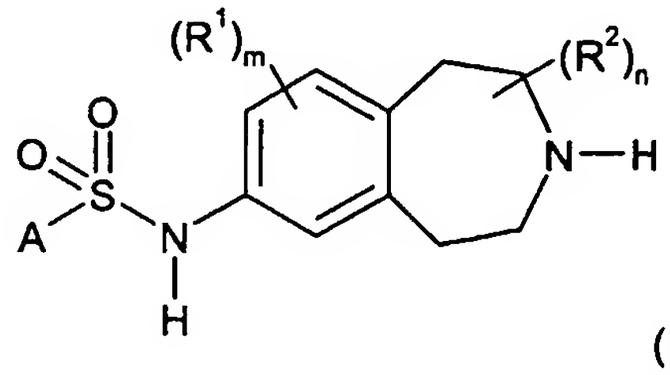
δH (MeOD, 400MHz) 2.99 (m, 4H), 3.14 (m, 4H), 3.55 (3H, s), 3.74 (3H, s), 6.70 (1H, s), 7.18 (1H, s), 7.52 (1H, s), 7.57 (1H, s)
Found $[MH]^+$ 431, 433, 435 ($C_{18}H_{20}Cl_2N_2O_4S$)

Pharmacological data

Compounds can be tested following the procedures outlined in WO98/27081.
The compounds of Examples E1-E17 were tested and showed good affinity for the 5-HT_6 receptor, having pKi values > 8 at human cloned 5-HT_6 receptors. More specifically, the compounds of Examples 6 and 10 demonstrated pKi values > 8.5 at human cloned 5-HT_6 receptors.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents hydrogen, halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $CONR^3R^4$ or $SO_2NR^3R^4$, wherein R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered aromatic or non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

R^2 represents hydrogen or C_{1-6} alkyl;

m represents an integer from 1 to 3;

n represents an integer from 1 to 4;

A represents phenyl, naphthyl or a monocyclic or bicyclic heteroaryl group each of which may be optionally substituted by one or more substituents which may be the same or different, and which are selected from those defined for R^1;

or solvates thereof.

2. A compound of formula (I) as defined in claim 1 wherein A represents phenyl or a monocyclic heteroaryl group optionally substituted by one or two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethoxy or trifluoromethyl groups.

3. A compound of formula (I) as defined in claim 2 wherein A represents phenyl disubstituted by halogen and 2-trifluoromethoxy.

4. A compound of formula (I) as defined in claim 3 wherein A represents phenyl disubstituted by 4-chloro or 4-bromo and 2-trifluoromethoxy.

5. A compound of formula (I) as defined in any one of claims 1 to 4 wherein m is 0.

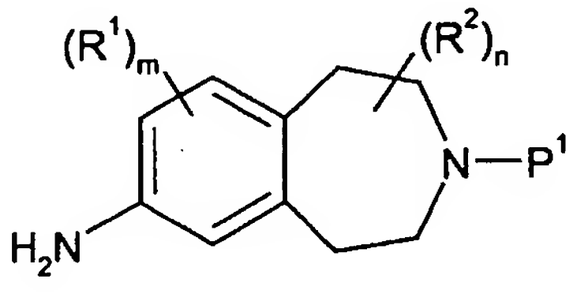
6. A compound of formula (I) as defined in any one of claims 1 to 5 wherein n is 0.

7. A compound of formula (I) as defined in claim 1 which is

2,3,4,5-Tetrahydro-7-(3-trifluoromethyl)phenylsulfonamido-1*H*-benzo[*d*]azepine;
7-Phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine;
2,3,4,5-Tetrahydro-7-(3-chloro)phenylsulfonamido-1*H*-benzo[*d*]azepine;
2,3,4,5-Tetrahydro-7-(5-bromo-2-thienyl)sulfonamido-1*H*-benzo[*d*]azepine;
2,3,4,5-Tetrahydro-7-(4-methyl)phenylsulfonamido-1*H*-benzo[*d*]azepine;
7-(4-Bromo-2-trifluoromethoxy)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine;
2,3,4,5-Tetrahydro-7-(2,3-dichloro)phenylsulfonamido-1*H*-benzo[*d*]azepine;
2,3,4,5-Tetrahydro-7-(3,5-dichloro-2-methoxy)phenylsulfonamido-1*H*-benzo[*d*]azepine;
2,3,4,5-Tetrahydro-7-(4-bromo-2-ethyl)phenylsulfonamido-1*H*-benzo[*d*]azepine;
7-(4-Chloro-2-trifluoromethoxy)phenylsulfonamido-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine;
7-(Benzenesulfonylamino)-9-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine;
7-(3-trifluoromethyl-benzenesulfonylamino)-9-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine;
7-(Benzenesulfonylamino)-9-bromo-1,2,4,5-tetrahydro-benzo[*d*]azepine;
7-(4-Bromo-2-trifluoromethoxy-benzenesulfonylamino)-6-chloro-1,2,4,5-tetrahydro-benzo[*d*]azepine;
3,5-Dichloro-2-methoxy-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yl)-benzenesulfonamide;
or a pharmaceutically acceptable salt thereof.

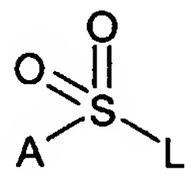
8. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

wherein R^1, R^2, m and n are as defined in claim 1 and P^1 is a suitable protecting group such as acetyl, trifluoroacetyl, *t*-butyloxycarbonyl, 2',2',2'-trichloroethoxycarbonyl, benzyl or methyl, with a compound of formula (III)



(III)

wherein A is as defined in claim 1 and L is a suitable leaving group, such as a halogen atom (eg. fluorine or chlorine) and thereafter deprotecting the resultant compound; or

(b) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(c) interconversion to other compounds of formula (I).

9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

10. A compound according to any one of claims 1 to 7 for use in therapy.

11. A compound according to any one of claims 1 to 7 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

12. The use of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

13. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 7 for use in the treatment of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

14. A method of treating depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia which comprises administering a safe and therapeutically effective amount to a patient in need thereof of a compound of formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof.

PCT/EP 03/01543

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D223/16 C07D409/12 A61K31/55 A61P3/04 A61P25/06
A61P25/08 A61P25/22 A61P25/24 A61P25/28 A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 02502 A (MOSS STEPHEN FREDERIK ;BROMIDGE STEVEN MARK (GB); SMITHKLINE BEECH) 21 January 1999 (1999-01-21) cited in the application claims 1,10 ---	1-14
A	WO 01 32646 A (BROMIDGE STEVEN MARK ;SERAFINOWSKA HALINA TERESA (GB); SMITHKLINE) 10 May 2001 (2001-05-10) cited in the application the whole document ---	1-14
A	US 5 939 451 A (BOES MICHAEL ET AL) 17 August 1999 (1999-08-17) column 1, line 63 -column 2, line 11; claim 1 ---	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2003	19/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schuemacher, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 089811 A (BROMIDGE STEVEN MARK ;MOSS STEPHEN FREDERICK (GB); SMITHKLINE BEEC) 14 November 2002 (2002-11-14) claims 1,12-15; example 1	1-14

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/01543

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902502 A	21-01-1999	AU 736256 B2	26-07-2001
		AU 9257898 A	08-02-1999
		BR 9810991 A	08-08-2000
		CN 1087294 B	10-07-2002
		CN 1261883 T	02-08-2000
		WO 9902502 A2	21-01-1999
		EP 0994862 A2	26-04-2000
		HU 0003073 A2	29-01-2001
		JP 2002511097 T	09-04-2002
		NO 20000108 A	10-01-2000
		NZ 501258 A	27-07-2001
		PL 338016 A1	25-09-2000
		TR 200000073 T2	21-06-2000
		TW 470743 B	01-01-2002
		US 6316450 B1	13-11-2001
		ZA 9806139 A	10-01-2000
WO 0132646 A	10-05-2001	AU 1278701 A	14-05-2001
		WO 0132646 A2	10-05-2001
		EP 1228066 A2	07-08-2002
US 5939451 A	17-08-1999	AT 205714 T	15-10-2001
		AU 694696 B2	23-07-1998
		AU 2841697 A	22-01-1998
		BR 9703788 A	17-11-1998
		CA 2209018 A1	28-12-1997
		CN 1170574 A ,B	21-01-1998
		CZ 9702002 A3	14-01-1998
		DE 59704640 D1	25-10-2001
		DK 815861 T3	21-01-2002
		EP 0815861 A1	07-01-1998
		ES 2163071 T3	16-01-2002
		HK 1007865 A3	30-04-1999
		HK 1007865 A1	03-05-2002
		HR 970349 A1	30-04-1998
		HU 9701096 A2	01-02-1999
		IL 121141 A	23-12-2001
		JP 3032176 B2	10-04-2000
		JP 10067734 A	10-03-1998
		KR 260480 B1	01-07-2000
		NO 972983 A	29-12-1997
		NZ 328146 A	28-10-1999
		PL 320822 A1	05-01-1998
		PT 815861 T	28-02-2002
		RU 2192257 C2	10-11-2002
		SG 77139 A1	19-12-2000
		TR 9700550 A2	21-01-1998
		US 6030976 A	29-02-2000
		US 5932599 A	03-08-1999
WO 02089811 A	14-11-2002	WO 02089811 A1	14-11-2002